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The European PKU Guidelines and the Challenges on Management Practices in Portugal

As Diretrizes Europeias para a PKU e os Desafios nas Práticas de Tratamento em Portugal

Cátia Filipa Pereira de Sousa

Orientado por: Dr.ª Manuela Ferreira de Almeida

Trabalho de Investigação

1.º Ciclo em Ciências da Nutrição

Faculdade de Ciências da Nutrição e Alimentação da Universidade do Porto

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ABSTRACT

Background: Phenylketonuria (PKU) management practices differ between and within countries. In 2007, the Portuguese Society for Metabolic Disorders (SPDM) approved the Portuguese Consensus (PC) for the nutritional treatment of PKU. The recently published European PKU Guidelines (EPG) aimed to improve patient care and harmonise treatment protocols in Europe.

Objective: To understand how the EPG will be accepted and implemented in Portuguese treatment centres.

Methods: An online questionnaire was prepared and the link was sent to 135 SPDM members. It highlighted the ten published key recommendations of EPG, comparing each statement with the information previously published on the PC. Responses were compiled and descriptive analyses performed.

Results: Twenty-five professionals responded to the questionnaire, and over half (56%) were nutritionists/dieticians. At least one questionnaire from each of the 10 national treatment centres was obtained. Only the recommendation regarding target phenylalanine (Phe) concentrations between 120-360 µmol/L for patients < 12 years received 100% consensus. The greatest concern was the recommendation regarding upper target blood Phe concentration for patients aged ≥ 12 years, with 48% considering that further discussion was needed before acceptance/rejection of this recommendation. All agreed that an open discussion was necessary to review the PC.

Conclusion: EPG received overall good acceptance but there was divided opinion on a few recommendations which require further discussion before being implemented in the Portuguese treatment centres.

Keywords: Phenylketonuria, PKU management, European PKU Guidelines, Portuguese Consensus

RESUMO

Introdução: O tratamento da Fenilcetonúria (PKU) difere entre e dentro dos próprios países. Em 2007, a Sociedade Portuguesa de Doenças Metabólicas (SPDM) aprovou o Consenso Português (PC) para o tratamento nutricional da PKU. As Diretrizes Europeias para a PKU (EPG) foram recentemente publicadas com o objetivo de melhorar o cuidado dos doentes e harmonizar os protocolos de tratamento na Europa.

Objetivo: Avaliar a aceitabilidade das EPG e como estas vão ser implementadas nos centros de tratamento portugueses.

Métodos: O *link* de um questionário elaborado *online* foi enviado para 135 sócios da SPDM. O questionário destacava as dez recomendações chave das EPG, comparando cada uma delas com a informação previamente publicada no PC. As respostas foram compiladas e foi realizada a análise descritiva dos dados.

Resultados: Vinte e cinco profissionais de saúde responderam ao questionário e mais de metade (56%) eram nutricionistas/dietistas. Foi obtido, pelo menos um questionário de cada um dos dez centros nacionais de tratamento. Apenas a recomendação sobre o intervalo da concentração sanguínea de fenilalanina (Phe) para os doentes com idade <12 anos reuniu 100% de consenso. A maior divergência existiu na recomendação sobre o limite máximo da concentração sanguínea de Phe para doentes com idade >12 anos, com 48% dos profissionais a considerarem ser necessário mais discussão antes de ser aceite ou rejeitada. Todos concordaram que será necessária uma discussão para a revisão do PC.

Conclusão: As EPG foram bem aceites no geral mas algumas recomendações, devido às diferentes opiniões encontradas necessitam de mais discussão antes de serem implementadas nos centros de tratamento portugueses.

Palavras-chave: Fenilcetonúria, Tratamento da PKU, Diretrizes Europeias para a PKU, Consenso Português

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LIST OF ABBREVIATIONS

EPG – European Phenylketonuria Guidelines

HCP – Health Care Professionals

PAH – Phenylalanine Hydroxylase Enzyme

PC – Portuguese Consensus

Phe – Phenylalanine

PKU – Phenylketonuria

SPDM – Portuguese Society for Metabolic Disorders

INTRODUCTION

Phenylketonuria (PKU) is an inherited metabolic disorder caused by deficiency in the phenylalanine (Phe) hydroxylase enzyme (PAH), which requires the cofactor tetrahydrobiopterin (BH4) to convert Phe to tyrosine (Tyr) [1]. PKU is the most frequent inherited metabolic disease of amino acid metabolism in Europe [2] with a frequency of 1 in 10000 newborn babies [3]. In Portugal, the prevalence of PKU at birth, until 2015, was 1:10512 newborns[4]. If left untreated, a patient with PKU will get a rapid and toxic accumulation of blood Phe that will cause severe brain damage [5]. Different levels of disease severity with different clinical outcomes have been identified and seem to be depend on the genotype [6]. The PAH deficiency is commonly classified based on the highest untreated blood Phe concentrations following a clinical diagnosis or at newborn screening [3]. Although it has some limitations, this classification has been used in Portugal[7].

Independently of the disease severity the main treatment objective is to reduce blood Phe concentrations [3]. A dietary Phe restriction to the minimum required for growth, supplemented with protein substitutes (PS) is the mainstay of treatment [5]. However, diet compliance is often poor, resulting in many practical challenges for patients and their families [8]. Other available nutritional treatment options include large neutral amino acids (LNAA) and glycomacropeptide (GMP) [9, 10]. The pharmacological treatment with the synthetic form of BH4 has also been showing an additional help to improve metabolic control and to increase Phe tolerance in a sub-group of patients [3, 11]. It is expected to maintain blood Phe concentrations within target range, although no consensual approach exists between different

European countries [12]. This is only one of the issues that clearly demonstrate the different management practices of PKU between countries [13].

By the end of the last century, some countries made an effort to have their own recommendations. In 1993, the Medical Research Council Working Party on PKU from United Kingdom published their recommendations on the dietary management of phenylketonuria [14]. Some years later, in 1997, a German working group for inborn errors of metabolism developed a survey towards a national guideline for the treatment of phenylketonuria [13]. In the United States, after almost seven years of attempting to set up guidelines, the National Institute of Health published their consensus in 2000 [15]. In 2005, the national PKU group and the physicians from regional centres established a nationwide guideline for France [16]. Other countries like Denmark, Poland and Hungry also had their position statements on PKU management [13].

The majority of these guidelines/position papers were focused on parameters such as screening, age at starting treatment, target blood Phe concentrations and frequency of blood Phe monitoring but the recommendations about diet practicalities were usually limited [12]. In that way, the existing practice is based on years of experience rather than on robust scientific evidence [17]. Therefore, internationally and evidence-based guidelines were needed in order to reach a standard of care [3, 18, 19].

More recently, in 2014 in the US, the American College of Medical Genetics and Genomics published recommendations for the diagnosis and clinical/nutritional management of PKU [20, 21]. These were developed from a summary of findings from a scientific review conference along with systematic literature review [22].

Some years later, in January 2017, a group of European experts in PKU with approval of the European Society for Phenylketonuria and Allied Disorders Treated as Phenylketonuria (ESPKU) published the first European Guidelines for the diagnosis and treatment of PKU (EPG). These were the result of three years of investigation with literature search, critical appraisal and evidence grading. EPG were divided in five main topics and highlighted ten key recommendations with highest priority for implementation to improve patient care and harmonise treatment protocols in Europe [3].

Specifically in Portugal, in 2007, the Portuguese Society for Metabolic Disorders (SPDM) approved the Portuguese Consensus (PC) for the nutritional treatment of PKU, developed by a group of specialists in the treatment of metabolic diseases and with many years of experience in PKU [7]. Most of the statements of PC should be followed by national treatment centres, although no objective data exists to confirm this.

OBJECTIVES

The present study aimed to understand how the recent published EPG will be accepted and implemented in the Portuguese treatment centres, through results obtained from a national questionnaire submitted to health care professionals (HCP) who work in the field of PKU. The main objective of this survey was to collect the opinion from HCP regarding each of the new EPG statements based on their professional experience, scientific evidence interpretation and their institutional management practices.

METHODS

A questionnaire was prepared under the agreement of the “PKU Think Tank” of SPDM using the online platform (*Google Forms)* in order to collect the opinion from HCP working in field of PKU in Portugal (Annex A). The questionnaire mainly relied on the ten key recommendations recently published in the EPG that were considered to have the highest priority for implementation. For each statement of the new EPG we performed a respective comparison with recommendations stated in the PC. The questionnaire consisted on 21 questions, 20 of them closed questions (answer choices provided) and one open question about the name of the National Reference Centre or the Institution that the HCP represent. The 21 questions were divided in three parts: Part A – Personal Data (essentially questions about professional activity); Part B – Described the ten Key European Guidelines and Part C – Final Considerations (a specific question asking for individual opinion about the importance to have a deep discussion towards the revision of the PC in the light of the new EPG). In questions regarding part B some of the answers provided the option “agree and will be implemented/is already implemented” and “do not agree but will be implemented/will not be implemented” in order to understand what were and will be some of the practice in PKU treatment centres.

Participants

The link to the questionnaire was sent by e-mail to all members of SPDM who got their e-mail addresses updated in the database (135 in total). It had to be sent to all members because it was not possible to discriminate in advance who worked in the field of PKU. On the e-mail with the invitation it was explained that only those

who work in the field should answer it. It was also requested to forward the link to other professionals/colleagues that although working in the field of PKU are not members of the SPDM. The survey was online between 31st March and 28th April 2017.

Data analysis

Responses were compiled in a spreadsheet and a statistical analysis was performed. Due to the nature and objective of the study, only descriptive analyses were performed in the form of sums (reported as percent of total responses). Although some HCP may have discussed the answers given with their colleagues from the same institution, we considered every answer as an individual opinion. For the overall objective of the paper, most attention was focused on questions concerning Part B, particularly the recommendations that will change the PKU management practices compared with those stated in the PC. We also considered mainly the percentages of agreement with each statement independently of being or not implemented in centres.

RESULTS

Twenty-five HCP responded to the questionnaire. The majority of responders were SPDM members (92%). Table 1 contains data about their professional experience. Over half (56%) were nutritionists/dieticians and 32% were medical doctors. From these, only one nutritionist was not SPDM member. There were also one psychologist and one biologist who responded to the questionnaire. Most of them

(91%) had clinical assistance as their main professional occupation and 88% followed-up infants and children.

Table 1. Personal data on professional experience.

		(%)
Academic Qualifications	Bachelor's	8
	Postgraduate	24
	Master's	32
	PhD	24
	Other	0
Length of professional experience	<5 years	12
	5-10 years	28
	10-20 years	32
	>20 years	28
Patients followed-up in centre	<10 patients	16
	10-25 patients	32
	25-50 patients	0
	50-100 patients	12
	>100 patients	40

Only four professionals did not identify their institution or centre. From those who identified their centres, the majority belong to centres located at north of the country but it was possible to obtain at least one questionnaire from each of the ten recognized treatment centres in Portugal. Table 2 shows the list of treatment centres and how many HCP from each one responded to the questionnaire. Almost half of responders (48%) classified the relevance of EPG with "Very high". Others 44% classified with "high".

Table 2. List of national Treatment Centres and the number of HCP from each one who responded to the questionnaire.

Treatment Centre	HCP
Centro Hospitalar do Porto, EPE	7
Centro Hospitalar Lisboa Norte, EPE (Hospital de Santa Maria)	3
Hospital do Divino Espírito Santo, Ponta Delgada	3
Centro Hospitalar de São João, EPE	2
Centro Hospitalar e Universitário de Coimbra, EPE (Centro Hospitalar de Coimbra e Hospitais da Universidade de Coimbra)	2
Centro Hospitalar de Vila Nova de Gaia, EPE	1
Centro Hospitalar de Lisboa Central, EPE	1
Centro Hospitalar do Funchal	1
Hospital de Santo Espírito, Angra do Heroísmo	1

Some of the answers concerning the key recommendations (Part B) showed a high percentage of agreement independently of being already implemented or not in the metabolic treatment centres. Recommendation presented in statement 2, which referred the importance of excluding BH4 deficiencies in differential diagnosis of hyperphenylalaninemia had 84% showing their agreement and the others 16% answered that had no opinion on this. The advice to all adults with PKU have life-long follow-up in specialised metabolic centres (statement 4) had 92% consensus. Recommendations on management of maternal PKU (statement 7 and 8) gathered 72% and 80% of agreement, respectively. Recommendation for a complete annual nutritional review for any patient with different degree of diet Phe restriction (statement 9) had 96% of agreement and only one professional disagreed. Almost all professionals (76%) agreed and will implement the recommendation about actions to be implemented when blood Phe concentrations

are out of range for a determinate period of time in patients younger than 12 years (statement 10). Only the recommendation regarding target Phe concentrations between 120-360 µmol/L for patients up to the age of 12 years (statement 5) received 100% consensus. All participants accepted the cut-off values and referred to follow these in their metabolic treatment centres. Out of the 10 EPG recommendations, three (statement 1, 3 and 6) showed a marked divided opinion. Recommendation regarding upper target blood Phe concentration for patients aged 12 years or older (statement 6), had 48% of HCP's considering that further discussion was needed before its acceptance or not. Figure 1 shows the distribution of answers provided to this question. Statement 3 about the management indications depending on Phe values and age also showed some inconsistency (Figure 2). Concerning the recommendation about diagnosis and classification of PAH deficiency (statement 1), almost one third (32%) failed to agree and preferred to keep the classification proposed by the PC (Figure 3). In Part C, all professionals agreed that an open discussion was necessary to support the review of the PC.

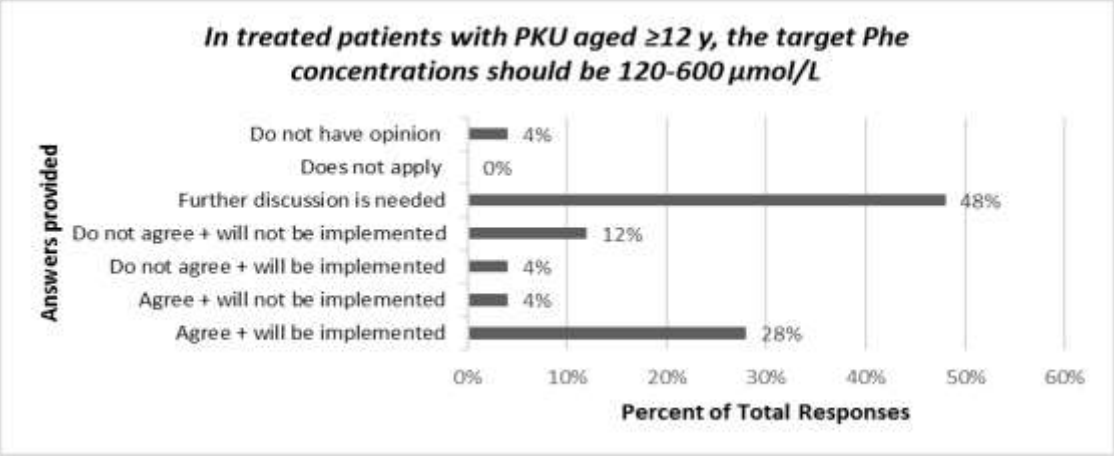

Figure 1. HCP opinion on EPG's statement 6.

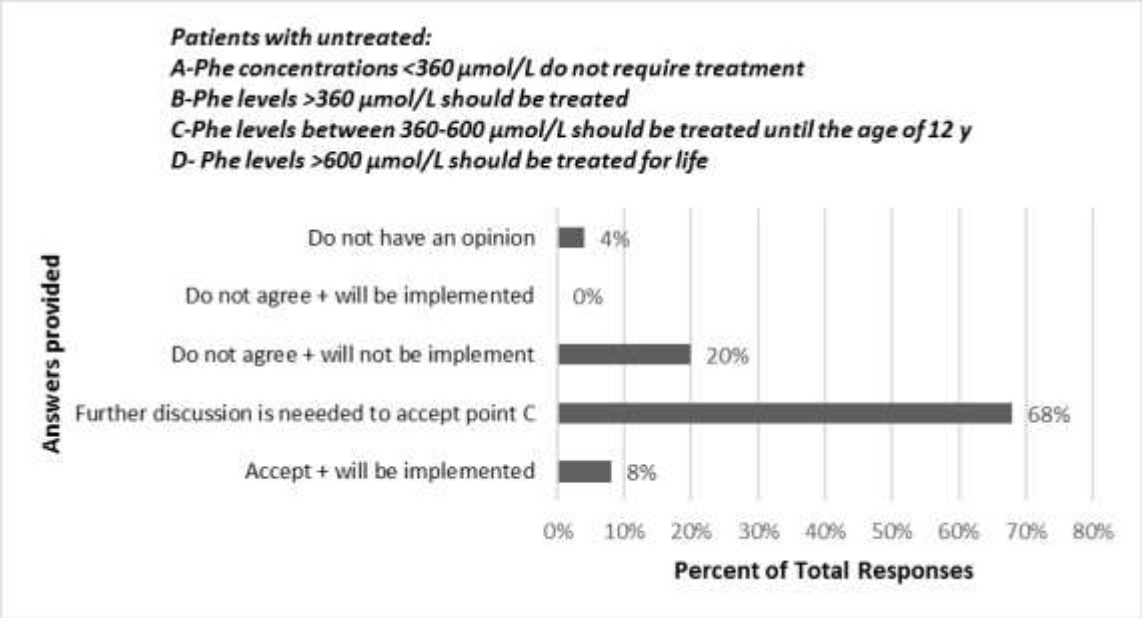

Figure 2. HCP opinion on EPG's statement 3.

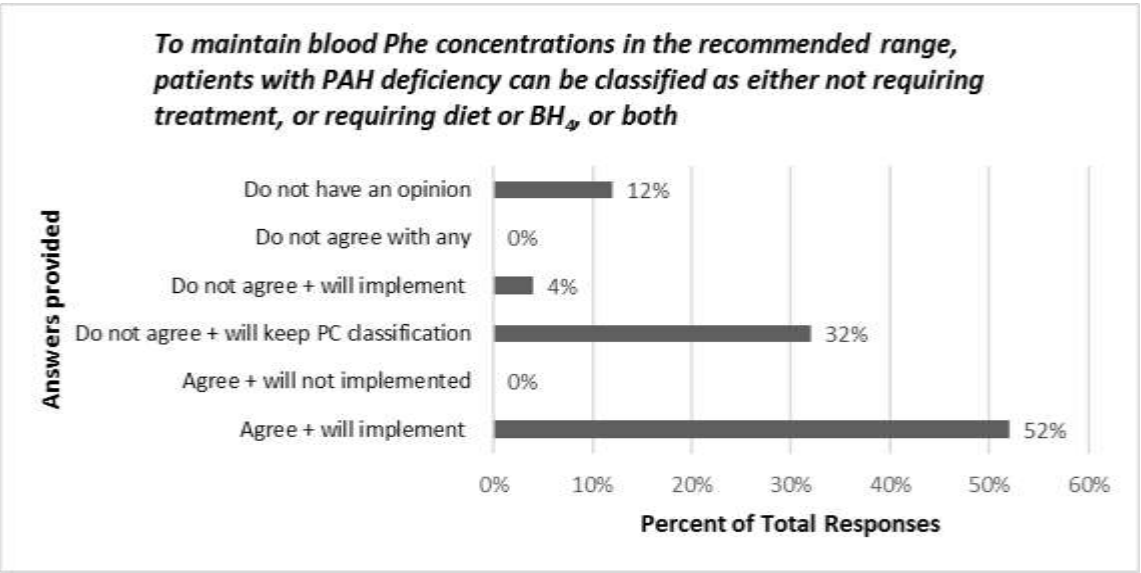

Figure 3. HCP opinion on EPG's statement 1.

DISCUSSION

The first important finding of this study is that the majority of EPG statements seem to have a good acceptance by Portuguese HCP. A great percentage underlined the high relevance of the EPG, underlining the need of an international guideline for standardised management of PKU. Another finding is that clinical management practices seem to differ across national treatment centres. This is in line with other studies that have suggested differences within other countries [12, 23]. As previously referred, the PC derived essentially from a consensus between a group of experts. Following that, its non-universal implementation will not be surprisingly. Questionnaires obtained were mainly answered by HCP working in the clinical field, which might be due to the fact of the EPG statements were focused in aspects related to clinical and nutritional management [3].

This study has some limitations. A low number of questionnaires were obtained and consequently the percentage of agreement should be carefully interpreted. However, Portugal is a small country and not all SPDM members are working in the field of PKU. In addition, the number of treatment centres is limited and few HCP are working in this field. Although it was obtained at least one questionnaire from the ten recognized national treatment centres, these results should be interpreted with care. We would be expecting to receive more responses from other HCP besides nutritionists/dieticians. The short time between EPG publication and the release of this survey may have prevent a higher participation of other HCP.

As long as we know this is the first study documenting the acceptance of the EPG towards its implementation in one European country. Other guidelines for other

inborn errors of metabolism have been published in the last years [24-26], but in very few cases the impact of these was systematically measured [27].

As it would be expected, some statements gathered a high percentage of agreement. Not only for being mentioned in PC but for the scientific evidence supporting them. All participants agreed with target Phe concentrations between 120 and 360 µmol/L until 12 years of age (statement 5). Blood Phe control in the first years of life is determinant for prognosis and is it universally accepted the benefits of early treatment [9]. Almost the totality also agreed with recommendations about the follow-up of adult patients through life in specialized centres (statement 4) and the annual nutritional review for patients in a restrict diet (statement 9). There is nowadays some concern about long-term health consequences in adult PKU patients [28-30] justifying the continuous follow-up in centralized treatment centres [31]. The treatment centre's organization in Portugal and the already existing agreement regarding annual nutritional review stated in the PC, probably both justified the high rank of agreement verified with these 2 statements. Although there had been no discussion in the PC, a great percentage showed their agreement about actions to be implemented when Phe values in patients younger than 12 years are out of range for a determinate time period (statement 10). The group of participants recognised the importance of dietary compliance in the first years of life making use from all the dietary strategies available [9]. Although recommendations about maternal PKU (statement 7 and 8) had more than 50% of agreement, we considered that this percentage would be higher. This might be explained by the fact that some HCP not follow this group of patients. Even though, these results should be kept in mind towards the

scheduling of continuous medical education programs for HCP working in this field.

In contrast with the statements receiving great agreement, others showed some controversy without consensus within the responders. Statements 1, 3 and 6 were those that seemed to be more controversial. It is important to emphasize that although EPG were evidence-based, different statements were ranked with different levels of evidence. Statements 3 and 6 had a “C grade” which means controversy evidence [3]. Therefore, we consider that this explain the results found in our survey. The target blood Phe concentration for patients aged or above 12 y proposed by the EPG (statement 6) is not in line with that referred in the PC: 600 vs. 480 µmol/L, respectively. Considering this, it is not surprising the wish for further discussion underlined by a great percentage of responders. There is some concern about the neurocognitive impairment seen with increased blood Phe concentrations [32, 33]. Even tough, there is a wide variation in terms of target blood Phe concentrations in different countries for this age group [1, 12]. While US guidelines advise 360 µmol/L as a target level [20, 21], the EPG proposed target is less stricter [3]. This lack of agreement between US and EPG guidelines may in part explain the difficulty of some HCP’s to immediately accept this recommendation. In statement 3, the fact of the majority mentioned that point C - “Patients with untreated Phe levels between 360-600 µmol/L should be treated until the age of 12 years”, needs more discussion may reflect their practical perception about the need to keep treatment after this age. Again, this result is expected since the PC recommends treatment for life when untreated blood Phe levels are greater than 360 µmol/L[7]. Although there is inconsistent evidence about this [32, 34] it derived from the necessity of good metabolic control especially

during the first 12 years of life [3]. Statement 1 also showed that a great percentage of disagreement with the new classification of PAH deficiency, probably highlighting the recent arrival of BH4 treatment in Portugal. Finally, statement 2 about the differential diagnosis of hyperphenylalaninemias also showed an unexpected result. Once this is a very important procedure, our vision is that universal agreement could have been reached. However, 16% mentioned that they did not have an opinion. Again, the continuous medical education may be important in order to harmonize knowledge and scientific debate between different treatment centres towards consensus in the PKU management practices.

CONCLUSION

The necessity of international guideline for management of PKU was unquestionable and the recent EPG aimed to set a standard of care for all patients. The majority of EPG statements gathered good acceptance but a deep discussion will be needed for its universal implementation in the Portuguese treatment centres. Under the agreement of the SPDM it will be needed a specific national meeting to discuss the revision process of the PC revision Our results support the idea that a methodological evaluation of the EPG implementation should occur in different European countries in order to clarify how long it will take to harmonize patient's care.

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Annexes

Annex A – Questionnaire

QUESTIONNAIRE: PKU EUROPEAN GUIDELINES: A NEW CHALLENGE

Despite the important advances of the last decades, the nutritional treatment proposed by Dr. Bickel more than 60 years ago remains the mainstay of treatment in patients with Phenylketonuria (PKU). There is no doubt that early diagnosis and treatment is crucial to achieve optimal outcome, but several aspects of the disease remain to be clarified. In order to fight the inconsistent management practices in Europe, the "Key European Guidelines for the Diagnosis and Management of Patients with Phenylketonuria" were just published in January 2017. With the aim to improve patient care and outcome and mainly to harmonize treatment protocols in European Countries, ten key recommendations were included in the guidelines.

These key recommendations were based either on evidence or on consensus when the grade of evidence was low or on the so-called good practice points. In total, 975 papers published up to Dec 31, 2015 were reviewed.

It may be controversial the recommended upper target phenylalanine blood concentration in particular situations. There are some differences when compared with the Portuguese Consensus, published in 2007 (Acta Pediátrica Portuguesa), followed by the majority of the Portuguese professionals involved in PKU management and with the American Guidelines, published in 2014 (Genet Med 2014;16: 188-200).

It seems to be mandatory to review the concepts that support our consensus. Therefore, a questionnaire was prepared to collect the opinions of those, who in somehow, are with their hands on the PKU patients management. This questionnaire is just the kick off for a big challenge that we must embrace: The National Review of the PKU Portuguese Consensus.

You can find the necessary documentation "Key European Guidelines….." and the Portuguese Consensus in the SPDM webpage under the item "recursos" (http://www.spdm.org.pt/recursos/protocolos-de-tratamento/).

Since it is important to start this discussion, please, take a few minutes of your time to answer this questionnaire.

We greatly appreciate your time and thank you very much in advance for your participation.

Note: This questionnaire was prepared by Cátia Sousa and Catarina Barbosa (Nutrition students) under the supervision of Doctor Júlio César Rocha and Dr. Manuela Ferreira de Almeida and with the collaboration of Prof. Anita MacDonald. Approved by the PKU Think Tank of the SPDM.

PART A – Personal Data

The questionnaire was sent to all members of the SPDM, due to logistic facility. If you do not work in the field of PKU management please give/forward this questionnaire to a colleague who is in the field.

Are you a member of the Portuguese Society of Metabolic Disorders (SPDM)?

- ◯ Yes
- ◯ No

1. Profession:

- ◯ Medical doctor
- ◯ Nutritionist/Dietitian
- ◯ Biochemist
- ◯ Psychologist
- ◯ Biologist
- ◯ Nurse
- ◯ Clinical Student
- ◯ Other:

2. Academic qualifications:

- ◯ Bachelor`s
- ◯ Postgraduate
- ◯ Master`s
- ◯ PhD
- ◯ Other:

3. Main professional occupation:

- ◯ Clinical assistance
- ◯ Laboratory
- ◯ Research
- ◯ Lecturing
- ◯ Other:

4. Length of professional experience in the field of PKU:

- ◯ Less than 5 years
- ◯ Between 5-10 years
- ◯ Between 10-20 years
- ◯ More than 20 years

5. Do you belong to a National Reference Centre for Inborn Errors of Metabolism? *

- ◯ Yes, please identify
- ◯ No, please identify the institution where you work

5.1 Please identify the National Reference Centre or the institution where you work:

6. How many patients are followed-up in your centre/institution?

- ◯ Less than 10 patients
- ◯ 10 to 25 patients
- ◯ 25 to 50 patients
- ◯ 50 to 100 patients
- ◯ More than 100 patients
- ◯ Does not apply, because I do not work in the clinical field

7. Please indicate the group(s) of patients that you follow-up (more than one option may apply):

- ☐ Infants and children (< 12 years of age)
- ☐ Adolescents (12-18 years of age)
- ☐ Adults (> 18 years of age)
- ☐ Pregnant women
- ☐ I do not work in the clinical field

8. How do you generally classify the relevance of the new Key European Guidelines for the diagnosis and treatment of PKU?

- ◯ Very high
- ◯ High
- ◯ Medium
- ◯ Low
- ◯ Very low
- ◯ I do not have an opinion

Please, now answer to Part B of this questionnaire

Part B - Key European Guidelines

The next questions are related to the recently published ten key recommendations for patients with PKU. We want to have your opinion about each statement.

Statement 1. (no possibility to assess the level of evidence because of a lack of any published work on this issue)

(a) To maintain blood phenylalanine concentrations in the recommended range, patients with phenylalanine hydroxylase (PAH) deficiency can be classified as:

- not requiring treatment
- requiring diet treatment
- requiring tetrahydrobiopterin (BH4) treatment
- requiring both diet and BH4 treatment

Portuguese Consensus:

" according to the neonatal blood phenylalanine concentration, the classification of PKU is considered:
- Hyperphenylalaninaemia: Blood [Phe] between 180 µmol/L (3 mg/dl) and 360 µmol/L (6 mg/dl)
- Moderate or atypical PKU: Blood [Phe] between 360 µmol/L (6 mg/dl) and 1200 µmol/L (20 mg/dl)
- Classical PKU: Blood [Phe] higher than 1200 µmol/L (20 mg/dl) "

- ( ) I agree with the new statement and my centre / institution will implement the new classification
- ( ) I agree with the new statement but it is not possible to implement this in my centre / institution
- ( ) I do not agree with the new statement and my centre / institution will keep the classification of Portuguese Consensus
- ( ) I do not agree with the new statement but my centre / institution will implement the new classification
- ( ) I do not agree with any of the classifications
- ( ) I do not have an opinion

Statement 2. (Grade of recommendation: high)

In the differential diagnosis of hyperphenylalaninaemia, of any degree, BH4 deficiencies should be excluded by measurement of pterins in blood or urine and dihydropteridine reductase activity in dried blood spot.

Note: In any child referred for hyperphenylalaninaemia, liver disease should also be excluded (pg. 3, Key European Guidelines)

This approach is consensually accepted for a long time and it is included in the Portuguese Consensus.

- ( ) I totally agree and we already implement this recommendation in our centre
- ( ) I totally agree but this recommendation is not performed in my centre
- ( ) I do not agree with this recommendation
- ( ) This new statement is not applicable to my centre / institution, due to lack of facilities
- ( ) I do not have an opinion

Statement 3. (Grade of recommendation: C; means controversy evidence, approved by consensus or the so-called good practice)

(a) Patients with untreated blood phenylalanine concentrations less than 360 µmol/L (6 mg/dl) do not requiretreatment.

(b) Patients with untreated blood phenylalanine levels more than 360 µmol/L (6 mg/dl) should be treated.

(c) Patients with untreated phenylalanine levels between 360 µmol/L (6 mg/dl) and 600 µmol/L (10 mg/dl) should be treated until the age of 12 years.
Providing blood Phe remains less than 600 µmol/L (10 mg/dl) without treatment afterwards (pg. 4, Key European Guidelines).

(d) Patients with untreated phenylalanine levels more than 600 µmol/L (10 mg/dl) should be treated for life.

Portuguese Consensus as well as American Guidelines (Genet Med 2014;16:188-200) recommend that: "Treatment should be applied and maintained throughout life when concentrations are greater than 360 µmol/L (6 mg/dl)."

The acceptance of statement in item (c) is less clear. It is a matter of controversy and the professional experience will be crucial for a consensus to be achieved.

- ( ) I accept the proposed cut-off points stated in the European Guidelines and these will be implemented in my centre / institution.
- ( ) To accept the proposed cut-off points, but statement c) needs further discussion.
- ( ) I do not agree with the new cut-off points and these will not be implemented in my centre / institution
- ( ) I do not agree with the new cut-off points but these will be implemented in my centre / institution.
- ( ) I do not have an opinion

Statement 4. (Grade of recommendation: C; means controversy evidence, approved by consensus or the so-called good practice)

(a) All adults with PKU should have life-long, systematic follow-up in specialised metabolic centres, because of specific risks that might occur during adulthood.

In the Portuguese Consensus, it is referred that a treatment for life approach should be adopted. However, there is no information regarding treatment centres organization and structure.

How do you judge the new statement proposal? (more than one option may apply).

- ☐ I agree with the new statement because I consider important to underline the utility of life-long follow-up in specialised metabolic centres
- ☐ I agree with the new statement and although it is not mentioned in Portuguese Consensus, it is already done in my centre / institution
- ☐ I do not agree with the new statement because I consider that adults can be followed in other kind of health services rather than in specialised centres
- ☐ This new statement does not apply to my centre / institution
- ☐ I do not have an opinion

Statement 5: (Grade of recommendation: B; means consensus)

(a) In treated patients with PKU up to the age of 12 years, target phenylalanine concentrations should be 120–360 µmol/L (2-6 mg/dl).

Portuguese Consensus also recommends that: up to 12 years old, blood phenylalanine concentrations should be within 120-360 µmol/L (2-6 mg/dl).

- ○ I totally agree and the recommendation is already implemented in my centre
- ○ I totally agree but the recommendation is not implemented in my centre
- ○ I do not agree but the recommendation is implemented in my centre
- ○ I do not agree and the recommendation is not implemented in my centre
- ○ This new statement does not apply to my centre / institution
- ○ I do not have an opinion

Statement 6. (Grade of recommendation: C; means controversy evidence, approved by consensus or the so-called good practice)

(a) In treated patients with PKU aged 12 years or older, the target phenylalanine concentrations should be 120–600 µmol/L (2-10 mg/dl).

Portuguese Consensus recommends that: after 12 years, the target blood phenylalanine concentrations should be within 120–480 µmol/L (2-8 mg/dl).

- ◯ I totally agree and this recommendation will be implemented in my centre
- ◯ I totally agree but this recommendation will not be implemented in my centre
- ◯ I do not agree but this recommendation will be implemented in my centre
- ◯ I do not agree and this recommendation will not be implemented in my centre
- ◯ To accept or reject this statement it will be needed further discussion
- ◯ This new statement does not apply to my centre / institution
- ◯ I do not have an opinion

Statement 7. (Grade of recommendation: B; means consensus)

(a) In pregnant patients treated for PKU the target phenylalanine concentrations should be 120–360 µmol/L (2-6 mg/dl).

Portuguese Consensus also recommends that: Pregnant women with PKU should maintain target blood phenylalanine concentrations between 120–360 µmol/L (2-6 mg/dL).

- ◯ I totally agree and the recommendation is already implemented in my centre
- ◯ I totally agree but the recommendation is not implemented in my centre
- ◯ I do not agree but the recommendation is implemented in my centre
- ◯ I do not agree and the recommendation is not implemented in my centre
- ◯ This new statement does not apply to my centre / institution
- ◯ I do not have an opinion

Statement 8. (Grade of recommendation: B; means consensus)

(a) Women with untreated blood phenylalanine concentrations less than 360 µmol/L (6 mg/dl) do not require treatment to lower blood phenylalanine before or during pregnancy

"In untreated women with Phe concentrations of more than 360 µmol/L (6 mg/dl), treatment is also required preconception and during pregnancy with the aim of reducing Phe concentration to less than 360 µmol/L (6 mg/dl)" (pg. 4, Key European Guidelines).

Portuguese Consensus only suggests that women who intend to become pregnant should adhere strictly to treatment even before stopping contraception measures.

- ◯ I consider the new statement important and it will be implemented in my centre / institution
- ◯ I consider that independently of blood phenylalanine concentrations, women who intend to become pregnant or already are pregnant should adhere strictly to treatment
- ◯ I do not agree with the statement because the value of cut-off is too high
- ◯ This new statement is not applicable to my centre / institution
- ◯ I do not have an opinion

Statement 9. (Grade of recommendation: C; means controversy evidence, approved by consensus or the so-called good practice)

(a) An annual nutritional review is required for any patient who is on a prescribed low phenylalanine diet or is self-restricting high protein foods. Such review must include a clinical examination including the anthropometric parameters (weight, height, BMI). We also recommended that plasma amino acids, plasma homocysteine or methylmalonic acid, haemoglobin, mean corpuscular volume, and ferritin are measured. All other micronutrients (vitamins and minerals including calcium, zinc, selenium) or hormones (parathyroid hormone) can be considered if clinically indicated.

The Portuguese Consensus suggests: in addition to the metabolic control, it is important to carry out a global analytical exploration with haematological, biochemical and renal and hepatic functions. These examinations must be carried out annually.

- ◯ I recognize the importance of an annual review but it is not performed in my centre / institution
- ◯ I recognize the importance of an annual review and it is performed in my centre / institution
- ◯ I do not agree with the annual review
- ◯ This new statement is not applicable to my daily practice because I do not work in the clinical field
- ◯ I do not have an opinion

Statement 10. (No possibility to assess the level of evidence because of a lack of any published work on this issue)

In patients younger than 12 years, when more than 50% of the phenylalanine concentrations are out of target range over a period of 6 months, consider:

(1) increased frequency of blood phenylalanine monitoring and outpatient visits and re-education,

(2) psychology consultation or social worker intervention, and

(3) hospital admission.

When around 100% of blood phenylalanine concentrations are out of target range over a period of 6 months and there are other signs of failure of adherence, such as lack of cooperation, clinic non-attendance, or unresolved issues outside PKU consider consultation with social services and child safeguarding measures.

In the Portuguese Consensus there is no specific information about this statement.

- ◯ I agree with the new statement but this will not be implemented in my centre / institution
- ◯ I agree with the new statement and it will be implemented in my centre / institution
- ◯ I do not consider this statement relevant and it will not be implemented in my centre / institution
- ◯ I do not consider this new statement relevant, but it will be implemented in my centre / institution
- ◯ This new statement is not applicable to my daily practice because I do not work in the clinical field
- ◯ I do not have an opinion

Part C - Final considerations

Given the relevance of Key European Guidelines do you agree that an open discussion should be taken into consideration to support the review of the Portuguese Consensus in the light of the new trends?

- ◯ Yes
- ◯ No
- ◯ I do not have an opinion